REMARKS

Claims 1-5 and 7-16 are pending. Claim 1-5 and 7-16 have been rejected. Claim 1 has been amended. No new matter has been added. Applicants are respectfully requesting reconsideration of the restriction requirement in view of the following remarks.

I. Withdrawn Objections/Rejections

Applicants acknowledge the withdrawal of the prior objection to claim 7 for referring to the amount of "reporter;" the rejection of claim 6 under 35 U.S.C. 102(b) as being anticipated by US Patent No. 5,861,315; and the rejection of claims 9 and 13 under 35 U.S.C. 102(b) as being anticipated by US Patent No. 5,639,618.

II. Rejection of Claims Under 35 U.S.C. §102

Claims 1-5 have been rejected under 35 U.S.C. 102(b) as being anticipated by U.S. Patent No. 5,665,557. It is suggested that the '557 patent teaches methods of obtaining an enriched population of human hematopoietic cells, separation of hematopoietic cells from a source, separating a subpopulation of cells utilizing a CDw109 antibody and then an additional marker to separate the cells, such as CD34, Thy-1 and rho. Limitations recited in instant claims 2-5 are suggested to be inherent in the cells of the '557 patent.

Applicants respectfully disagree with this rejection. In addition to CD34, Applicants have identified a particular collection of markers that are specifically expressed by self-renewing, multipotent, slow-cycling cells. These markers are disclosed throughout the specification and more particularly in

Tables 1-7. However, the collection of selected slow-cycling cell markers provided in the instant specification does not include the CDw109 marker disclosed the '557 patent. Accordingly, in an earnest effort to distinguish the present invention from the teachings of the '557 patent, Applicants have amended claim 1 to clarify that that selected slow-cycling cell marker employed therein is selected from the group of Transcription Factor 3, Transcription Factor 4, Nuclear Factor of Activated T-cells Cytoplasmic 1, Alpha 6 Integrin, G-Protein-Coupled Receptor 49 and Bone Morphogenetic Protein Receptor 1A. Support for Transcription Factor 3 (Tcf3) and Transcription Factor 4 (Tcf4) as markers of slow-cycling cells is found in Table 7 at page 47 and the Accession numbers associated therewith. Support for Nuclear Factor of Activated T-cells Cytoplasmic 1 (NFATc1) as a marker of slow-cycling cells is found in Table 1 at page 16. Support for Alpha 6 Integrin as a marker of slow-cycling cells is found at page 34, lines 13-18 of the specification. Support for G-Protein-Coupled Receptor 49 (GPR49) and Bone Morphogenetic Protein Receptor 1A (BMPR1a) as markers of slow-cycling cells is found in Table 6 at pages 44 and 45 and the Accession numbers associated therewith.

"A claim is anticipated only if each and every element as set forth in the claim is found, either expressly or inherently described, in a single prior art reference." *Verdegaal Bros. v. Union Oil Co. of California*, 814 F.2d 628, 631, 2 USPQ2d 1051, 1053 (Fed. Cir. 1987).

In so far as the '557 patent fails to teach or suggest the method and cells as presently claimed, it is respectfully requested that this rejection be withdrawn.

III. Rejection of Claims Under 35 U.S.C. §103

Claims 7 and 9 stand rejected under 35 U.S.C. 103(a) as being unpatentable over U.S. Patent No. 5,639,618 when taken with Strathdee et al. ((1999) *Gene* 229:21-29) and Bohl et al. ((1997) *Nat. Med.* 3:229-305) when taken with Mahmud ((2001) *Blood* 97:3061-3068) and U.S. Patent 6,485,971. In response to Applicants arguments filed June 9, 2009, the Examiner cites *Ex parte Smith* in support of the assertion that KSR forecloses the argument that a specific teaching, suggestion, or motivation is required to support a finding of obviousness. The Examiner contends that the combination of art as a whole is sufficient to arrive at the claimed invention. It is suggested that the '618 document, Strathdee and Bohl teach guidance for utilizing the nucleic acid sequences found in parts a)-c) of claim 7. With regard to parts d)-g) of claim 7, it is suggested that Mahmud et al. provide specific guidance to show that multipotent stem cells, such as hematopoietic stem cells, are considered slow-cycling cells. The Examiner concludes that one of skill in the art would recognize that stem cells are slow-cycling cells and that enriching steps, such as those taught in the '971 document are also known in the art. It is suggested that Mahmud teach that pluripotent cells are slow cycling, which would clearly maintain higher levels of reporter protein than cells that are dividing, and the '971 document provides clear guidance as to how to separate cells that have higher versus lower levels of protein expression. The Examiner contends that one of skill in the art would be further motivated, in view of the teachings of Mahmud and the '971 document, to inactivate the regulatable transcription factor (by, for example, the withdrawal of

doxycycline in the case of using the Tet system), and select for slow-cycling stem cells by allowing the cells to divide, and selecting cells that contain a higher level of reporter protein expression, wherein one of ordinary skill in the art would have been sufficiently motivated to make this modification in order to produce substantially pure populations of stem cells.

Applicants respectfully traverse this rejection. The question of obviousness is resolved on the basis of underlying factual determinations including (1) the scope and content of the prior art, (2) any differences between the claimed subject matter and the prior art, (3) the level of skill in the art, and (4) where in evidence, so-called secondary considerations. *Graham v. John Deere Co.*, 383 U.S. 1, 17-18, 148 USPQ 459, 467 (1966).

In the instant case, there are considerable differences between the present invention and the combined teachings of the cited references. Indeed, the Examiner acknowledges that neither the '618 document, Srathdee or Bohl teach inactivating the steps of d) inactivating the regulatable transcription factor so that expression of the reporter protein is decreased; e) incubating the cell for a sufficient amount of time so that the cell goes through one or more cell cycles to generate a population of cells; f) detecting the amount of reporter protein in the population of cells; and g) sorting the population of cells by the amount of reporter protein present in each cell (paragraph bridging pages 8 and 9 of the Office Action). To compensate for these deficiencies, it is suggested that Mahmud et al. teach that pluripotent cells are slow-cycling and maintain higher levels of reporter protein and the '971 document provides clear guidance for separating cells that have higher versus lower levels of

protein expression. However, Applicants respectfully assert that combined teachings of Mahmud et al. and the '971 document would not have provided the necessary guidance or suggested to one skilled in the art steps d)-g) as presently claimed.

Mahmud teaches analyzing the replicative history of pluripotent hematopoietic stem cells (PHSC) in baboons by continuously administering bromodeoxyuridine (BrdU) (see abstract). Subpopulations of bone marrow cells were isolated by Hoechst/Rhodamine staining and $CD34^+$ selection (see Figure 1) and the BrdU content of different subsets was determined every 2 to 5 weeks (see page 3063, section entitled "Analysis of BrdU incorporation and propidium iodide staining"). U.S. Patent 6,485,971 teaches a method of enriching for a viable subpopulation of epidermal cells having an altered proliferative potential compared with an unfractionated population of epidermal cells based upon a higher level of a cell surface integrin expression and expression of transerrin receptor, EGFR, IGFR or keratinocyte growth factor receptor (see claim 1). Thus, collectively, these references would have suggested to the skilled artisan that dye exclusion in combination with cell surface protein expression can be used to sort cells. However, neither of these references would have suggested to the skilled artisan that cells can be sorted based upon the amount of reporter protein present in each cell in the manner presently claimed. Indeed, nowhere is there the suggestion that cells can be sorted based upon cell cycle-mediated dilution or retention of a reporter protein. In this respect, nowhere is any guidance in either Mahmud et al. or the '971 document of inactivating a regulatable transcription factor so that expression of a reporter

protein is decreased, *i.e.*, step d) of the claimed method. Accordingly, while the Examiner has relied upon the combined teachings of Mahmud et al. and the '971 document to provide the guidance for carrying out steps d)-g) of claim 7 (see paragraph bridging pages 6 and 7 of the Office Action), these references simply fall short of providing the necessary teachings to have suggested the claimed method.

In this respect, Applicants respectfully assert that *Ex parte Smith* does not in fact foreclose the argument that a suggestion or motivation is required to support a finding of obviousness. As stated in *Ex parte Smith*:

> *KSR* forecloses Appellant's argument that a specific teaching is required for a finding of obviousness. *KSR*, 127 S. Ct. at 1741, 82 USPQ2d at 1396.

A proper rejection under 35 U.S.C. 103(a) still requires a determination as to whether there was an apparent reason to combine the known elements in the fashion claimed. *Id.* at 1740-41, 82 USPQ2d at 1396. The Court noted that "[t]o facilitate review, this analysis should be made explicit. *Id.* (citing *In re Kahn,* 441 F.3d 977, 988, 78 USPQ2d 1329, 1336 (Fed. Cir. 2006)).

In the instant case, the Examiner has not set out an articulated rationale for combining the disparate teachings of the cited references to arrive at the claimed invention. Indeed, the mere conclusory statement that one would have been motivated to inactivate the regulatable transcription factor and select for slow-cycling stem cells by allowing the cells to divide, and selecting cells that contain a higher level of reporter protein expression based upon the teachings of Mahmud and the '971 document (page 7, ¶1 of the Office Action) is simply not

supported by teachings of these references. Therefore, there is reversible error in this rejection under 35 U.S.C. 103(a) and it is respectfully requested that this rejection be withdrawn.

Claims 8 and 10-14 have been rejected under 35 U.S.C. 103(a) as being unpatentable over U.S. Patent No. 5,639,618 when taken with Strathdee et al. and Bohl et al. when taken with Mahmud and U.S. Patent 6,485,971 as applied to claims 7 and 9, and further in view of U.S. Patent No. 5,665,557.

Claims 15-16 have been rejected under 35 U.S.C. 103(a) as being unpatentable over Strathdee et al. and Bohl, et al. when taken with Mahmud et al. and U.S. Patent No. 6,485,971 and U.S. Patent No. 5,665,557 as applied to claims 7-14 above, and further in view of U.S. Patent No. 5,861,315.

Applicants respectfully traverse the rejection of claims 8 and 10-16 in view of the cited documents. If an independent claim is nonobvious under 35 U.S.C. 103, then any claim depending therefrom is nonobvious. *In re Fine*, 837 F.2d 1071, 5 USPQ2d 1596 (Fed. Cir. 1988). As Applicants have indicated, the combined teachings of the cited references are simply insufficient to establish a *prima facie* case of obviousness against base claim 7. Accordingly, claims 8 and 10-16, which depend from claim 7 cannot be held obvious. It is therefore respectfully requested that these rejections under 35 U.S.C. 103(a) be reconsidered and withdrawn.

IV. Conclusion

Applicants believe that the foregoing comprises a full and complete response to the Office Action of record. Accordingly, favorable reconsideration and subsequent allowance of the pending claims is earnestly solicited.

Respectfully submitted,

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